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Multicomponent Synthesis of 2-(Alkylsulfanyl)-4-[furan-2-yl-(or thiophen-2-yl)]-5,6,7,8-tetrahydroquinoline-3-carbonitriles

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Abstract—Substituted 2-(alkylsulfanyl)-4-[furan-2-yl(or thiophen-2-yl)]-5,6,7,8-tetrahydroquinoline-3-carbonitriles were synthesized by condensation of furfural or thiophene-2-carbaldehyde with 2-cyanoethanethioamide, 1-(cyclohex-1-en-1-yl)pyrrolidine, and alkyl halides. The structure of methyl 2-{[3-cyano-4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinolin-2-yl]sulfanyl}acetate was determined by X-ray analysis.

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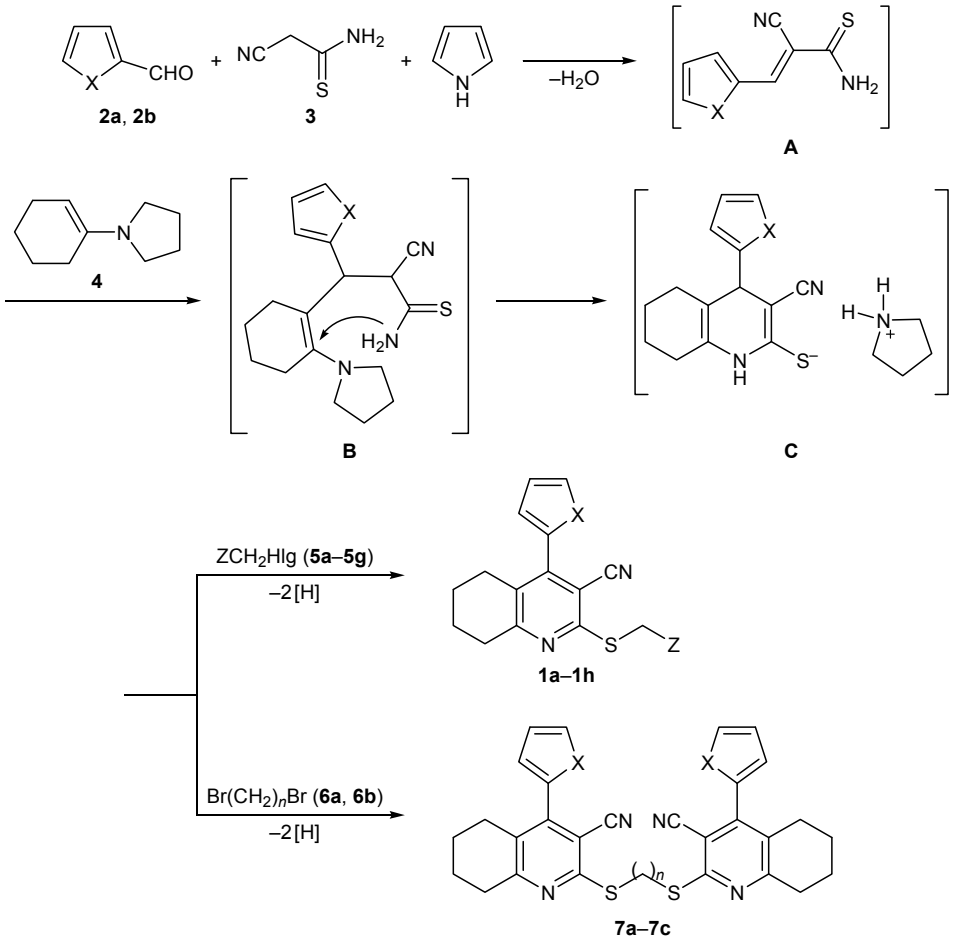
Multicomponent syntheses have become more and more popular among synthetic organic chemists due to the possibility of using this methodology for the preparation of both fairly simple compounds and fused heterocyclic systems [1–3]. Such reactions offer a number of advantages as compared to multistep syntheses, in particular simple experimental procedures, quantitative yields of the final products, and environmental safety [4, 5]. We previously synthesized in this way functionalized pyridines [6, 7], spiro 1,4-dihydropyridines [8, 9], and functionally substituted 1,4-dihydro-1,6-naphthyridines [10, 11] and pyrido[2,3-*d*]-pyrimidine [12].

We now report a multicomponent synthesis of 2-alkylsulfanyl-4-[furan-2-yl(or thiophen-2-yl)]-5,6,7,8-tetrahydroquinoline-3-carbonitriles **1a**–**1h** that are potential intermediate products for the preparation of calcium channel blockers [13], eukaryotic elongation factor-2 kinase (eEF-2K) inhibitors [14], and drugs for the treatment of atherosclerosis [15], inflammations [16], and other human diseases [17]. The reaction of heteroaromatic aldehyde **2a** or **2b** with 2-cyanoethanethioamide (**3**), 1-(cyclohex-1-en-1-yl)pyrrolidine (**4**), and alkyl halides **5a**–**5g** in ethanol at 20°C afforded substituted 5,6,7,8-tetrahydroquinolines **1a**–**1h** (Scheme 1). This reaction is likely to involve intermediate formation of 2-cyano-2-[furan-2-yl(or thiophen-2-yl)methylidene]ethanethioamide **A** which alkylates enamine **4** according to Stork [18], yielding adduct **B**. Intramolecular transamination [19] of the latter gives pyrrolidinium salt **C**, and the subsequent alkylation with alkyl halides **5a**–**5g** leads to final sulfides **1a**–**1h**. When α,ω-dibromoalkanes **6a** and **6b** (0.5 equiv) were added instead of alkyl halides **5**, the products were substituted bis(5,6,7,8-tetrahydroquinolin-2-ylsulfanyl)alkanes **7a**–**7c**.

The structure of compounds **1a**–**1h** and **7a**–**7c** was confirmed by spectral data. Their IR spectra contained an absorption band at 2215–2224 cm^{-1} due to stretching vibrations of the conjugated cyano group and carbonyl band at 1674–1714 cm^{-1}. The number and position of signals in the ^{13}C NMR spectra of **1a**, **1h**, and **7b** were consistent with the assumed structures. In the mass spectra of the synthesized compounds we observed the molecular ion peaks $[M + 1]^+$. Signals from protons in the tetramethylene fragment, heteroaromatic substituents, and alkyl groups were present in the ^1H NMR spectra. The SCH_2 protons characteristically resonated as a singlet at δ 2.60–4.46 ppm [6–9].

The structure of methyl 2-{[3-cyano-4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinolin-2-yl]sulfanyl}acetate (**1a**) was determined by X-ray analysis (see figure). The planar thiophene ring in molecule **1a** is almost orthogonal to the pyridine ring [the corresponding

Scheme 1.



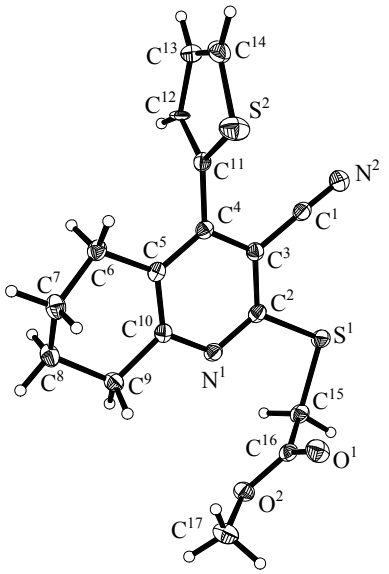
1, X = S, Z = COOMe (**a**), CN (**b**); X = O, Z = $CONH_2$ (**c**), cyclopropylcarbonyl (**d**); X = S, Z = H (**e**), cyclopropylcarbonyl (**f**), Ph (**g**); X = O, Z = 2-oxochromen-3-ylcarbonyl (**h**); **2**, X = O (**a**), S (**b**); **5**, Hlg = Cl, Z = COOMe (**a**), CN (**b**), $CONH_2$ (**c**); Hlg = Br, Z = cyclopropylcarbonyl (**d**); Hlg = I, Z = H (**e**); Hlg = Cl, Z = Ph (**f**); Hlg = Br, Z = 2-oxochromen-3-ylcarbonyl (**g**); **6**, *n* = 2 (**a**), 3 (**b**); **7**, X = S, *n* = 2 (**a**); X = O, *n* = 3 (**b**); X = S, *n* = 3 (**c**).

dihedral angle is 88.6(1)°]. The other geometric parameters of molecule **1a** were consistent with reference values [20].

EXPERIMENTAL

The IR spectra were recorded in KBr on a Perkin Elmer Spectrum One spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker DRX 500 spectrometer at 499.95 and 125.74 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were obtained on an Agilent MSDSL mass-selective detector (electron impact; samples were introduced in a trifluoroacetic acid matrix). The elemental compositions were determined on a Perkin Elmer CHN analyzer. The melting points were measured on a Kofler hot stage. The progress of reactions and the purity of products were monitored by TLC on Silufol UV254 plates using acetone–hexane (3 : 5) as eluent; spots were developed by treatment with iodine vapor or under UV light.

X-Ray diffraction data for compound 1a. $C_{17}H_{16}N_2O_2S_2$ (*M* 344.44); monoclinic crystal system; unit cell parameters (at 100 K): *a* = 10.9844(4), *b* = 8.8673(4), *c* = 16.4879(7) Å; β = 91.318(1)°; *V* = 1605.5(1) $Å^3$; space group $P2_1/n$; *Z* = 4; d_{calc} = 1.425 g/cm^3. Total of 14539 reflection intensities were measured on a Bruker SMART APEX diffractometer [21] at 100 K (λMoK_α radiation, $2\theta_{max}$ = 54.20°) from a 0.21×0.19×0.17 mm single crystal of **1a**. Averaging of equivalent reflections left 3509 independent reflections (R_{int} = 0.0218) which were used for the structure solution and refinement. A correction for absorption



Structure of the molecule of methyl 2-{[3-cyano-4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinolin-2-yl]sulfanyl}acetate (**1a**) according to the X-ray diffraction data.

(μ 0.342 mm^{-1}) was applied, the transmission factors being determined by SADABS [22], T_{max} = 0.944, T_{min} = 0.932. The structure was solved by the direct method; all non-hydrogen atoms were localized by the difference syntheses of electron density and were refined against F^2_{hkl} in anisotropic approximation. All hydrogen atoms were placed into geometrically calculated positions which were refined according to the riding model [U(H) = 1.2 or 1.5U(C), where U(C) is the equivalent temperature factor of the corresponding carbon atom]. Final divergence factors: R_1 = 0.0376 [F_{hkl}; 3180 reflections with $I > 2\sigma(I)$], wR_2 = 0.1063 (F^2_{hkl}; 3509 reflections); goodness of fit 1.017. All calculations were performed using SHELXTL software package [23].

2-(Alkylsulfanyl)-4-hetaryl-5,6,7,8-tetrahydroquinolin-3-carbonitriles 1a–1h (*general procedure*). Three drops of pyrrolidine were added under stirring at 20°C to a mixture of 10 mmol of aldehyde **2a** or **2b** and 1.0 g (10 mmol) of 2-cyanoethanethioamide (**3**) in 20 mL of ethanol. The mixture was stirred for 15 min, 1.5 g (10 mmol) of enamine **4** was added, the mixture was stirred for 30 min, a solution of 10 mmol of alkyl halide **5a**–**5g** in 15 mL of DMF was added, and the mixture was stirred for 1 h and left to stand for 24 h. The mixture was then diluted with an equal volume of water, and the precipitate was filtered off and washed with water, ethanol, and hexane.

Methyl 2-{[3-cyano-4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinolin-2-yl]sulfanyl}acetate (1a). Yield 2.8 g (82%), light yellow crystals, mp 124–125°C (from EtOH) [24]. ^{13}C NMR spectrum, δ_C, ppm: 21.59, 21.87, 26.50, 32.15, 32.98, 52.38, 104.51, 115.08, 127.82, 128.02, 129.33, 129.86, 133.66, 146.78, 157.04, 161.63, 169.20. Mass spectrum: m/z 345 (I_{rel} 100%) $[M + 1]^+$. Calculated: M 344.457.

2-[(Cyanomethyl)sulfanyl]-4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (1b). Yield 2.3 g (75%), yellow powder, mp 158–160°C (from AcOH). IR spectrum, ν, cm^{-1}: 2222, 2249 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.51–1.96 m (4H, CH_2), 2.56 t (2H, CH_2, J = 5.5 Hz), 2.98 t (2H, CH_2, J = 6.3 Hz), 4.23 s (2H, SCH_2), 7.01–7.19 m (2H, 3′-H, 4′-H), 7.77 d (1H, 5′-H, J = 3.7Hz). Mass spectrum: m/z 312 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 61.65; H 4.12; N 13.32. $C_{16}H_{13}N_3S_2$. Calculated, %: C 61.71; H 4.21; N 13.49. M 311.431.

2-{[3-Cyano-4-(furan-2-yl)-5,6,7,8-tetrahydroquinolin-2-yl]sulfanyl}acetamide (1c). Yield 2.1 g (68%), yellow powder, mp 195–197°C (from 1-BuOH). IR spectrum, ν, cm^{-1}: 3380, 3260, 3205 (NH_2), 2218 (C≡N), 1674 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.68–1.80 m (2H, CH_2), 1.82–1.94 m (2H, CH_2), 2.70 t (2H, 5-H, J = 6.1 Hz), 2.93 t (2H, 8-H, J = 6.6 Hz), 3.87 s (2H, SCH_2), 6.68 d (1H, 3′-H, J = 1.8 Hz), 6.97 d.d (1H, 4′-H, J = 3.5 Hz), 7.06 br.s and 7.43 br.s (1H each, NH_2), 7.88 d (1H, 5′-H, J = 1.8 Hz). Mass spectrum: m/z 314 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 61.28; H 4.71; N 13.33. $C_{16}H_{15}N_3O_2S$. Calculated, %: C 61.40; H 4.83; N 13.41. M 313.379.

2-[(2-Cyclopropyl-2-oxoethyl)sulfanyl]-4-(furan-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (1d). Yield 2.4 g (71%), yellow powder, mp 142–144°C (from EtOH). IR spectrum, ν, cm^{-1}: 2224 (C≡N), 1702 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.83–0.96 m (4H, CH_2, cyclopropane), 1.68–1.75 m (2H, CH_2), 1.77–1.82 m (2H, CH_2), 2.19–2.32 m (1H, CH, cyclopropane), 2.72 t (2H, 5-H, J = 6.0 Hz), 2.88 t (2H, 8-H, J = 6.2 Hz), 4.21 s (2H, SCH_2), 6.68 d (1H, 3′-H, J = 4.8 Hz), 6.93–7.02 m (1H, 4′-H), 7.88 d (1H, 5′-H, J = 1.2 Hz). Mass spectrum: m/z 339 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 67.31; H 5.22; N 8.16. $C_{19}H_{18}N_2O_2S$. Calculated, %: C 67.43; H 5.36; N 8.28. M 338.431.

2-(Methylsulfanyl)-4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (1e). Yield 2.2 g (79%), yellow crystals, mp 135–137°C (from AcOH). IR spectrum: ν 2219 cm^{-1} (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.55–1.66 m (2H, CH_2), 1.73–1.82 m (2H, CH_2), 2.60 s (3H, Me), 2.82–2.93 m (4H, CH_2), 7.18–

7.29 m (2H, 3′-H, 4′-H), 7.83 d (1H, 5′-H, J = 4.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.20, 22.12, 22.33, 26.90, 33.60, 115.66, 127.72, 128.16, 129.56, 130.08, 134.23, 146.94, 159.12, 162.06. Mass spectrum: m/z 287 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 62.78; H 4.80; N 9.66. $C_{15}H_{14}N_2S_2$. Calculated, %: C 62.90; H 4.93; N 9.78. M 286.418.

2-[(2-Cyclopropyl-2-oxoethyl)sulfanyl]-4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (1f). Yield 2.4 g (68%), yellow crystals, mp 141–143°C (from EtOH). IR spectrum, ν, cm^{-1}: 2217 (C≡N), 1704 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.87–1.12 m (4H, CH_2, cyclopropane), 1.62–1.73 m (2H, CH_2), 1.79–1.88 m (2H, CH_2), 2.21–2.34 m (1H, CH, cyclopropane), 2.54 t (2H, CH_2, J = 5.4 Hz), 2.88 t (2H, CH_2, J = 6.5 Hz), 4.22 s (2H, SCH_2), 7.16–7.24 m (2H, 3′-H, 4′-H), 7.75 d (1H, 5′-H, J = 3.7 Hz). Mass spectrum: m/z 355 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 64.25; H 5.00; N 7.78. $C_{19}H_{18}N_2OS_2$. Calculated, %: C 64.38; H 5.12; N 7.90. M 354.495.

2-(Benzylsulfanyl)-4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (1g). Yield 3.1 g (85%), yellow powder, mp 122–124°C (from AcOH). IR spectrum: ν 2223 cm^{-1} (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.69–1.79 m (2H, CH_2), 1.81–1.96 m (2H, CH_2), 2.70 t (2H, CH_2, J = 6.5 Hz), 2.99 t (2H, CH_2, J = 5.9 Hz), 4.46 s (2H, SCH_2), 6.67 d (1H, 3′-H, J = 4.5 Hz), 6.94 d.d (1H, 4′-H, J = 5.2 Hz), 7.22 t (1H, Ph, J = 7.1 Hz), 7.27 t (2H, Ph, J = 7.1 Hz), 7.40 d (2H, Ph, J = 7.2 Hz), 7.84 d (1H, 5′-H, J = 3.6 Hz). Mass spectrum: m/z 363 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 69.45; H 4.88; N 7.60. $C_{21}H_{18}N_2S_2$. Calculated, %: C 69.58; H 5.00; N 7.73. M 362.518.

4-(Furan-2-yl)-2-{[2-oxo-2-(2-oxo-2*H*-chromen-3-yl)ethyl]sulfanyl}-5,6,7,8-tetrahydroquinoline-3-carbonitrile (1h). Yield 3.3 g (75%), yellow finely crystalline powder, mp 235–237°C (from 1-BuOH). IR spectrum, ν, cm^{-1}: 2219 (C≡N); 1714, 1692 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.54–1.73 m (4H, CH_2), 2.65 t (2H, CH_2, J = 5.3 Hz), 3.36–3.44 t (2H, CH_2, J = 6.2 Hz), 4.77 s (2H, SCH_2), 6.77 d (1H, 3′-H, J = 2.6 Hz), 7.06 d.d (1H, 4′-H, J = 2.3 Hz), 7.45 t (1H, H_{arom}, J = 7.4 Hz), 7.51 d (1H, H_{arom}, J = 8.3 Hz), 7.78 t (1H, H_{arom}, J = 8.3 Hz), 7.96 d (1H, H_{arom}, J = 7.8 Hz), 8.00 d (1H, 5′-H, J = 1.2 Hz), 8.77 s (1H, 5″-H). ^{13}C NMR spectrum, δ_C, ppm: 21.47, 21.87, 26.52, 32.89, 36.32, 101.34, 112.19, 115.46, 116.33, 118.21, 124.22, 125.24, 126.32, 130.91, 134.87, 140.84, 145.53, 145.98, 147.93, 154.65, 157.81, 158.51, 161.81, 191.41. Mass spectrum: m/z 443 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 67.71; H 3.96; N 6.25. $C_{25}H_{18}N_2O_4S$. Calculated, %: C 67.86; H 4.10; N 6.33. M 442.490.

Substituted bis(5,6,7,8-tetrahydroquinolin-2-ylsulfanyl)alkanes **7a**–**7c** were synthesized following the general procedure but using 5 mmol of α,ω-dibromoalkane **6a** or **6b**.

2,2′-[Ethane-1,2-diylbis(sulfanediyl)]bis[4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile] (7a). Yield 2.0 g (70%), yellow finely crystalline powder, mp 272–274°C (from 1-BuOH). IR spectrum: ν 2217 cm^{-1} (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.61–1.73 m (4H, CH_2), 1.76–1.84 m (4H, CH_2), 2.52 t (4H, CH_2, J = 5.6 Hz), 2.86 t (4H, CH_2, J = 5.9 Hz), 3.67 s (4H, SCH_2), 7.21–7.26 m (4H, 3′-H, 4′-H), 7.82 d (2H, 5′-H, J = 2.7 Hz). Mass spectrum: m/z 571 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 62.98; H 4.44; N 9.75. $C_{30}H_{26}N_4S_4$. Calculated, %: C 63.13; H 4.59; N 9.82. M 570.825.

2,2′-[Propane-1,3-diylbis(sulfanediyl)]bis[4-(furan-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile] (7b). Yield 2.0 g (75%), light yellow powder fluorescing under UV irradiation, mp 177–179°C (from 1-BuOH). IR spectrum: ν 2215 cm^{-1} (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.54–1.68 m (4H, CH_2), 1.72–1.82 m (4H, CH_2), 2.03–2.14 m (2H, C**H**$_2$CH$_2$S), 2.59–2.64 m (4H, CH_2), 2.73–2.85 m (4H, CH_2), 3.34–3.46 m (4H, SCH_2), 6.75 br.s (2H, 3′-H), 7.02 br.s (2H, 4′-H), 7.98 br.s (2H, 5′-H). ^{13}C NMR spectrum, δ_C, ppm: 21.59 (2C), 21.96 (2C), 26.58 (2C), 28.30 (2C), 28.48, 33.22 (2C), 101.80 (2C), 112.10 (2C), 115.22 (2C), 115.65 (2C), 125.84 (2C), 140.77 (2C), 145.38 (2C), 146.12 (2C), 158.71 (2C), 161.77 (2C). Mass spectrum: m/z 553 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 63.19; H 4.98; N 9.97. $C_{31}H_{28}N_4O_2S_2$. Calculated, %: C 67.37; H 5.11; N 10.14. M 552.720.

2,2′-[Propane-1,3-diylbis(sulfanediyl)]bis[4-(thiophen-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile] (7c). Yield 1.9 g (65%), yellow powder, mp 135–137°C (from AcOH). IR spectrum: ν 2216 cm^{-1} (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.63–1.72 m (4H, CH_2), 1.76–1.88 m (4H, CH_2), 2.12 t (2H, C**H**$_2$CH$_2$S, J = 6.8 Hz), 2.55 t (4H, CH_2, J = 5.9 Hz), 2.89 t (4H, CH_2, J = 6.0 Hz), 3.38 t (4H, SCH_2, J = 6.8 Hz), 7.16 d (2H, 3′-H, J = 2.0 Hz), 7.21 d.d (2H, 4′-H, J = 4.2 Hz), 7.75 d (2H, 5′-H, J = 4.0 Hz). Mass spectrum: m/z 585 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 63.54; H 4.73; N 9.42. $C_{31}H_{28}N_4S_4$. Calculated, %: C 63.66; H 4.82; N 9.58. M 584.853.

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